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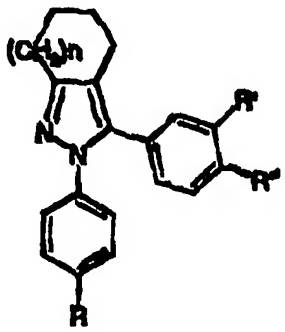
(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING DIARYL–CYCLOMETHYLENPYRAZOLE COMPOUNDS AND THEIR USE AS CYCLOOXYGENASE I (COX I) INHIBITORS

(57) Abstract

A pharmaceutical composition comprising a diaryl–cyclomethylenpyrazole compound of formula (I) wherein n is 0, 1, 2 or 3; R, R' and R'', equal to or different from each other, are H, halogen, alkylsulphonyl, aminosulphonyl and alkylaminosulphonyl, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.



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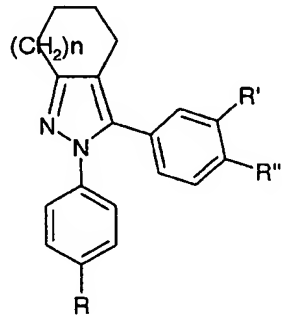
PHARMACEUTICAL COMPOSITIONS COMPRISING DIARYL-CYCLOMETHYLENPYRAZOLE COMPOUNDS AND THEIR USE AS CYCLOOXYGENASE I (COX I) INHIBITORS

* * * * * * * *

The present invention relates to pharmaceutical compositions comprising a diaryl-cyclomethylenpyrazole compound endowed with anti-inflammatory, analgesic and antipyretic activity, the process for the preparation of said diaryl-cyclomethylenpyrazole compounds and some novel diaryl-cyclomethylenpyrazole compounds thus obtained.

More particularly, the present invention relates to a pharmaceutical composition comprising a diaryl-cyclomethylenpyrazole of general formula



(I)

wherein

n is 0,1, 2 or 3;

R, R' and R", equal or different each other, are H, halogen, alkylsulphonyl, aminosulphonyl and alkylaminosulphonyl,

or a pharmaceutically acceptable salt thereof,

together with at least a pharmaceutically acceptable carrier.

It is known that non-steroidal anti-inflammatory drugs, usually used for treating inflammation, pain and fever exhibit their major activity by inhibiting the cyclooxygenase enzyme (COX).

Recently, two isoforms of the enzyme have been found: the first one (COX1) is constitutively expressed in a large variety of cells while the

second one (COX2) is rapidly induced in several type of cells by agents such as endotoxines and cytokines.

The constitutive form COX1 is responsible in large part of the basal endogenous release of prostaglandins that promote physiological actions such as maintaining the gastrointestinal integrity or the renal blood flux.

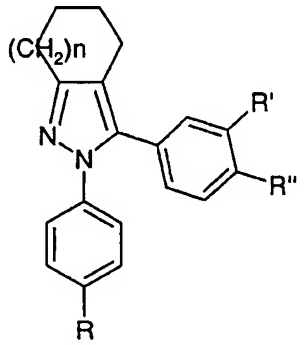
On the contrary, the inducible form COX2 is likely responsible of the production of prostaglandins in replay to pro-inflammatory stimuli in different type of tissues and cells.

For this reasons, the person skilled in the art opines that a selective inhibitor of COX2 has anti-inflammatory properties like to a conventional non-steroid anti-inflammatory, however with reduced ulcerogenic and nephrotoxic action. A short description of the potential utilities of COX2 inhibitors is given in the article by J.Vane in "Nature", 367, 215-216, 1994, and in an article on "Drugs News and Prospectives", 7, 501-512, 1994.

Now, it has been found that the compounds of formula (I) are provided with high selectivity towards COX2.

Some diaryl-cyclomethylenpyrazoles of formula (I) are novel.

It is therefore a second object of the present invention to provide a diaryl-cyclomethylenpyrazole of formula (Ia)



(Ia)

wherein

n is 0,1, 2 and 3;

R, R' and R", equal or different each other, are H, halogen, alkylsulphonyl, aminosulphonyl and alkylaminosulphonyl,
or pharmaceutically acceptable salts thereof,
provided, however, that

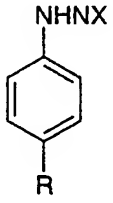
a) when n is 1, and two of R, R' and R" are hydrogen, the third is not hydrogen or chlorine; and
b) when n is 3, at least one of R, R' and R" is not hydrogen.

Preferably, n is 0,1 or 2.

Examples of preferred halogens are fluorine and chlorine.

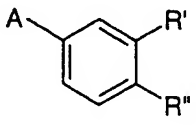
Preferably, the alkyl chain of the alkylsulphonyl and alkylamino sulphonyl has of from 1 to 6 and, more preferably, of from 1 to 3 carbons and may be linear, branched or cyclic. Typical examples of such substituents are methysulphonyl, methylaminosulphonyl and cyclopropylsulphonyl.

A third object of the present invention is to provide a process for manufacturing a compound of formula (I), characterized in that a compound of formula



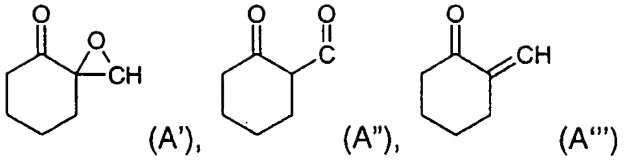
(II)

wherein X is H or cyclohexyliden, and R has the above mentioned meanings, is reacted with a compound of formula



(III)

wherein R' and R" have the above mentioned meanings and A is selected from the group comprising COHal, A', A" and A"'



(A'), (A"), (A"')

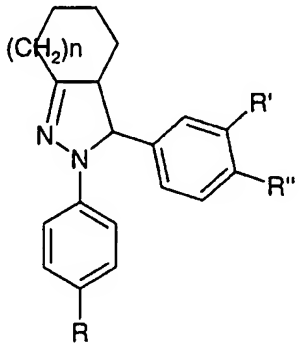
wherein Hal is halogen, preferably chlorine.

Preferably, when X = H, this reaction is carried out in a solution of a suitable polar diluent and in the presence of an organic or mineral acid at a temperature of from 0 to 120°C. Preferably, of from 60 to 80°C. Typical examples of preferred diluents are lower aliphatic alcohols.

When A = A' and X is hydrogen, the reaction is preferably carried out in a solution of a lower alcohol, preferably ethyl alcohol, in the presence of an acid, preferably glacial acetic acid, according to A.J. Nunn and F.J. Rowell in "J. Chem. Soc.", 23, 2435-8, 1975, to give directly the desired compound of formula (I).

In turn, when A = A" and X is hydrogen, the reaction is preferably carried out in a solution of a lower alcohol, preferably ethyl alcohol, in the presence of an acid, preferably sulphuric acid, to give, as main product, the desired compound of formula (I).

Finally, when A = A"' and X is hydrogen, the reaction is preferably carried out in a solution of a lower alcohol, preferably ethyl alcohol, in the presence of an acid, preferably hydrochloric acid, to give the compound of formula



(IV)

from which the corresponding compound of formula (I) is prepared by treating with a weak oxidant, such as bromine in water, according to the method described in J. Chin. Chem. Soc., 41, 585-9, 1994, or with manganese bioxide in a solution of methylenechloride.

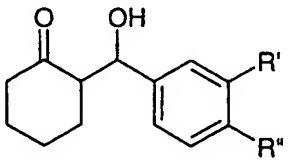
The compound of formula (IV) wherein n = 1, R = methylsulphonyl, R' = H and R" = Cl is novel. Therefore, it is a further object of the present invention.

When A is COHal and X is cyclohexylidene, the reaction is preferably carried out in the presence of anhydrous tetrahydrofuran at a temperature of from -70 to 20°C to give directly the compound of formula (I).

The intermediate compounds of formula (III) wherein A is A', R' is H and R" is alkylsulphonyl, preferably methylsulphonyl, or fluorine, the compound wherein A is A', R' and R" are halogen, preferably chlorine and fluorine, and the compound of formula (III) wherein A = A"', R' = H and R" is alkylsulphonyl, preferably methylsulphonyl, are new.

Therefore, they are a further object of the present invention.

The new compounds of formula (III) wherein A is A"' and R' and R" have the above mentioned meanings, are preferably prepared by dehydration of the compound of formula



(V)

The compound of formula (V), wherein R' is H and R" is alkylsulphonyl, preferably methysulphonyl, is also new and it is a further object of the present invention.

Typical examples of diseases which might benefit from the treatment with a pharmaceutical composition according to the present invention

are the inflammatory diseases such as, for example, Alzheimer disease, ulcerative colitis and colon tumor.

Preferably, the pharmaceutical compositions of this invention are prepared in a suitable dosage form comprising an effective dose of at last a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least an inert pharmaceutically acceptable carrier.

Examples of suitable dosage forms are tablets, capsules, coated tablets, granules, liposomes, solutions and syrups for oral administration; creams, liposomes, ointments and medicated patches for topical administration; suppositories for rectal administration and sterile solutions for injectable, aerosolic and ophthalmic administration.

The dosage forms may also contain other conventional ingredients such as: preservatives, stabilizers, surface-active agents, buffers, salts for the regulation of the osmotic pressure, emulsifiers, sweeteners, colouring agents, flavouring agents and the like.

When required by particular therapies, the pharmaceutical composition of the present invention may contain other pharmacologically active ingredients whose concomitant administration is therapeutically useful.

The amount of the compound of formula (I) or of a pharmaceutically acceptable salt thereof in the pharmaceutical composition of the present invention may vary in a rather wide range depending on known factors such as, for instance, the type of disease to be treated, the severity of the disease, the body weight of the patient, the dosage form, the chosen route of administration, the number of dosage forms administrated daily and the efficacy of the chosen compound of formula (I). However, the optimum amount may be easily and routinely determined by a person skilled in the art.

Typically, the amount of the compound of formula (I) or of a pharmaceutically acceptable salt thereof in the pharmaceutical composition of

the present invention will be such that it insures an administration level of from 0.01 to 140 mg/Kg/day.

The dosage forms of the pharmaceutical composition of the present invention can be prepared according to techniques which are known to the pharmaceutical chemist and comprise procedures such as mixing, granulation, compression, solubilization, sterilization and the like.

The following examples are intended to illustrate the present invention without limiting it in any way.

EXAMPLE 1

Preparation of 2-(α-hydroxy-4-methysulphonylbenzyl) cyclohexanone

(V: R' = H, R" = SO_2CH_3)

An aqueous solution (20.6 ml) of sodium carbonate (1.89 g, 0.018 mole) was added dropwise to a mixture of 4-methysulphonylbenzalaldehyde (2.21 g, 0.012 mole) and cyclohexanone (4.7 g, 0.048 mole) at room temperature. After 10 minutes at room temperature, the reaction mixture was diluted with water (135 ml) and allowed to stand for 6 additional hours. The solid precipitated was filtered and crystallized from ethyl acetate, obtaining 2 g of the desired product (m.p. 150-152°C).

Elemental analysis	C	H
% found:	59.42	6.35
% calculated: for $C_{14}H_{18}O_4S$	59.56	6.43

^{1}H-NMR (δ, $CDCl_3$): 1.5-2.7 (m, 9H); 3.08 (s, 4H); 5.46 (m, 1H); 7.5 (d, 2H); 7.8 (d, 2H).

EXAMPLE 2

Preparation of 2-(4-methylsulphonyl)benzylidencyclohexanone

(III: A = A"', R' = H, R" = SO_2CH_3)

A solution of 2-(α-hydroxy-4-methylsulphonylbenzyl) cyclohexanone (4.84 g, 0.017 mole) in absolute ethyl alcohol (9.7 ml), added with one drop of concentrate HCl, was heated up to the reflux temperature. After some minutes, it was cooled, dilued by an equal volume of water and

extracted with dichloromethane (2x10 ml). After evaporation of the solvent under reduced pressure, the residual was chromatographed on a flash column, eluting with a mixture of toluene:ethyl acetate 4:1. Yield, 1.33 g (m.p. 89-90°C).

Elemental analysis	C	H
% found:	63.45	6.17
% calculated: for $C_{14}H_{16}O_3S$	63.62	6.10

^{1}H-NMR (δ, $CDCl_3$): 1.7-2.2 (m, 4H); 2.5-2.9 (m, 4H); 3.08 (s, 3H); 7.5-7.7 (m, 3H); 7.8-8.1 (d, 2H).

EXAMPLE 3

Preparation of 2-(4-methylsulphonyl)phenyl-3-(4-chlorophenyl)-4,5,6,7-tetrahydroindazole (AFR 906)

(I: n = 1, R = SO_2CH_3, R' = H, R" = Cl)

a) Glacial acetic acid (15 ml) was quickly dropped under stirring and at room temperature into a suspension of 4-methylsulphonylphenyl hydrazine (7.3 g, 0.039 mole) and 2'-(4-chlorophenyl)spiro [cyclohexane-2'-oxiran]-2-one (9.2 g, 0.039 mole) in absolute ethyl alcohol (400 ml). Then, the reaction mixture was heated at reflux for 4 hours. The solvents were removed under reduced pressure and the residue was crystallized two times from ethyl alcohol. Yield, 11.4 g (m.p. 153-155°C).

Further preparations of AFR 906 performed as decribed above melted at 176-178°C. Under microscope, the compound melting at 153-155°C proved to be in form of birefractive prismatic tablets, while the compound melting at 176-178°C was in form of non-refractive microcrystals.

Elemental analysis	C	H	N
% found:	61.93	4.81	7.12
% calculated: for $C_{20}H_{19}ClN_2O_2S$	62.08	4.95	7.24

^{1}H-NMR (δ, DMSO): 1.6-1.9 (m, 4H); 2.4-2.7 (m, 4H); 3.25 (s, 3H); 7.1-7.6 (m, 6H); 7.8 (d, 2H).

b) Condensation of 2-(4-chlorobenzoyl)cyclohexanone with 4-methylsulphonylphenylhydrazine afforded a mixture that was separated by column chromatography to give, as main product, the compound mentioned in paragraph a) above.

c) Oxidation, preferably with MnO_2, in solution of CH_2Cl_2 of the compound of the Example 7 (AFR 109).

By working in a way similar to that described above may be prepared the following compounds:

AFR 206: 2-(4-methylsulphonyl)phenyl-3-(4-chlorophenyl)-4,5,6,7,8-2H-pentahydrocycloeptapyrazole (I: n =2, R = SO_2Me, R' = H, R" = Cl), m.p. 171-3°C (hexane-ethyl acetate)

AFR 207: 2-(4-aminosulphonyl)phenyl-3-(4-chlorophenyl)-4,5,6,7,8-2H-pentahydrocycloeptapyrazole (I: n =2, R = SO_2NH_2, R' = H, R" = Cl), m.p. 200-1°C (hexane-ethyl acetate)

AFR 209: 2-(4-cyclopropylsulphonyl)phenyl-3-(4-chlorophenyl)-4,5,6,7-tetrahydroindazole (I: n = 1, R = cyclopropyl-SO_2, R' = H, R" = Cl), m.p. 136-8°C (ethanol)

AFR 402: 2-(4-methylsulphonyl)phenyl-3-(4-chlorophenyl)-2,4,5,6-tetra hydrocyclopentapyrazole (I: n =0, R = SO_2Me, R' = H, R" = Cl), m.p. 185-7°C (hexane-ethyl acetate)

AFR 404: 2-(4-aminosulphonyl)phenyl-3-(4-chlorophenyl)-2,4,5,6-tetra hydrocyclopentapyrazole (I: n =0, R = SO_2NH_2, R' = H, R" = Cl), m.p. 251-3°C (ethyl acetate)

AFR 405: 2-(4-methylsulphonyl)phenyl-3-(3-chloro-4-fluorophenyl)-4,5,6,7-tetrahydroindazole (I: n =1, R = SO_2Me, R' = Cl, R" = F), m.p. 187-9°C (hexane-ethanol)

AFR 406: 2-(4-aminosulphonyl)phenyl-3-(3-chloro-4-fluorophenyl)-4,5,6,7-tetrahydroindazole (I: n =1, R = SO_2NH_2, R' = Cl, R" = F), m.p. 238-240°C (ethanol)

AFR 408: 2-(4-chlorophenyl)-3-(4-methylsulphonyl)phenyl-4,5,6,7-tetra hydroindazole (I: n = 1, R = Cl, R' = H, R" = SO_2Me), m.p. 181-2°C (ethyl acetate)

AFR 500: 2-(4-aminosulphonyl)phenyl-3-(4-methyphenyl)-4,5,6,7-tetrahydroindazole (I: n =1, R = SO_2NH_2, R' = H, R" = CH_3), m.p. 180-1°C (absolute ethanol)

AFR 507: 2-(4-aminosulphonyl)phenyl-3-(3-chlorophenyl)-4,5,6,7-tetrahydroindazole (I: n =1, R = SO_2NH_2, R' = Cl, R" = H), m.p. 239-240°C (absolute ethanol)

AFR 508: 2-(4-aminosulphonyl)phenyl-3-(4-methoxyphenyl)-4,5,6,7-tetrahydroindazole (I: n =1, R = SO_2NH_2, R' = H, R" = OCH_3), m.p. 168-170°C (ethyl acetate)

AFR 601: 2-(4-methysulphonyl)phenyl-3-phenyl-4,5,6,7-tetrahydroindazole (I: n =1, R = SO_2Me, R' = R" = H), m.p. 151-2°C (hexane-ethyl acetate)

AFR 602: 2-(4-aminosulphonyl)phenyl-3-phenyl-4,5,6,7-tetrahydroindazole (I: n =1, R = SO_2NH_2, R' = R" = H), m.p. 189-191°C (ethanol)

EXAMPLE 4

Preparation of 2-(4-aminosulphonyl)phenyl-3-(4-chlorophenyl)-4,5,6,7-tetrahydroindazole (AFR 101)

(I: n = 1, R = SO_2NH_2, R' = H, R" = Cl)

By working in a way similar to that described in paragraph a) of Example 3, 1.8 g of the desired product (m.p. 195-197°C, from ethyl acetate) were obtained from 2'-(4-chlorophenyl)spiro[cyclohexane-2'-oxirane]-2-one (2.37 g) (J. Chem. Soc. "Perkin I" page 2435, 1975) and from (4-aminosulphonyl)phenylhydrazine (1.87 g).

Elemental analysis	C	H	N
% found:	58.92	4.64	10.89
% calculated: for $C_{19}H_{18}ClN_3O_2S$	58.83	4.68	10.83

^{1}H-NMR (δ, DMSO): 1.6-2.0 (m, 4H); 2.4-2.8 (m, 4H); 7.1-7.6 (m, 6H+2); 7.8 (d, 2H).

EXAMPLE 5

Preparation of 2'-(4-fluorophenyl)spiro[cyclohexane-2'-oxiran]-2-one

(III: A = A', R' = H, R" = F)

A solution of 30% H_2O_2 (6.54 ml) and, after some minutes, a solution of NaOH 6N (3.1 ml) were dropped into a solution of 2-(4-fluoro)benzylidencyclohexanone (2.8 g, 0.0136 mole) in methyl alcohol (17 ml) under stirring at 10°C. When the dropping was over, after 1 hour at 10°C, the reaction mixture was slowly warmed to room temperature and maintained at this temperature for further 2 hours. After removal of the impurities by filtration, H_2O (50 ml) was added to the limpid solution for precipitating a solid that was dried and crystallized from ethyl acetate (6.5 ml). Yield, 0.9 g (m.p. 137-139°C).

Elemental analysis	C	H
% found:	70.76	5.83
% calculated: for $C_{13}H_{13}FO_2$	70.89	5.95

^{1}H-NMR (δ, $CDCl_3$): 1.2-2.9 (m, 8H); 4.0 (s, 1H); 6.9-7.4 (m, 4H).

EXAMPLE 6

Preparation of 2-(4-methylsulphonyl)phenyl-3-(4-fluorophenyl)-4,5,6,7-tetrahydroindazole (AFR 108)

(I: n = 1, R = SO_2CH_3, R' = H, R" = F)

By working in a way similar to that described in paragraph a) of the previous Example 3, 12.7 g of the desired product (m.p. 183-185°C, from ethyl alcohol) were obtained from 2-(4-fluorophenyl)spiro [cyclohexane-2'-oxirane]-2-one (8.6 g) prepared according to the previous Example 6.

Elemental Analysis	C	H	N
% found:	64.67	5.14	7.54
% calculated: $C_{20}H_{19}FN_2O_2S$	64.85	5.17	7.50

^{1}H-NMR (δ, DMSO): 1.6-1.9 (m, 4H); 2.4-2.6 (m, 4H); 3.2 (s, 3H); 7.1-7.6 (m, 6H); 7.8 (d, 2H).

EXAMPLE 7

Preparation of 2-(4-methylsulphonyl)phenyl-3-(4-chlorophenyl)-3,3a,4,5,6,7-hexahydroindazole (AFR 109)

(IV; n = 1, R = SO_2CH_3, R' = H, R" = Cl)

2-(4-chlorobenzyliden)cyclohexanone (6.2 g, 0.028 mole) was added to a solution of (4-methylsulphonyl)phenylhydrazine hydrochloride (6.13 g, 0.024 mole) in absolute ethyl alcohol (200 ml) and, after 1 hour at room temperature, the solution was heated at reflux. After 1 hour, the solution was evaporated under reduced pressure and the residue was taken up with ethyl ether. After filtering, the solid precipitate was crystallized to give 3.3 g of the desired product (m.p. 168-170 °C).

Elemental analysis	C	H	N
% found:	61.94	5.49	7.14
% calculated: for $C_{20}H_{21}ClN_2O_2S$	61.77	5.44	7.20

^{1}H-NMR (δ, $CDCl_3$): 0.6-2.5 (m, 7H); 2.7-3.0 (m, 1H); 3.0 (s, 3H); 3.2-3.6 (td, 1H); 5.2 (d, J=12Hz, 1H), 6.8-7.7 (m, 8H).

TEST 1

In vitro activity on Cyclooxygenase 1 and 2

The activity of the compounds of formula (I) on cyclooxygenase 1 and 2 was evaluated *in vitro* using cell lines that selectively produce one or the other one enzyme.

As a source of cyclooxygenase 1 (COX1), it was used the U 937 human cell line, while the J 774.2 murine cell line was employed, after lipopolysaccharide (LPS) stimulation, for the cyclooxygenase 2 (COX2). The activity of the compound under evaluation was measured as ability

of inhibiting the transformation of arachidonic acid into prostaglandines (in particular E2 prostaglandin).

In order to analyze the activity on COX1, the U 937 cells were plated at the concentration of $1x10^6$/ml on a Dulbecco's Modified Eagle Medium (DMEM) free of serum and the compound under evaluation was added at the desired concentration (10-0.001 μM). After incubation for 5 minutes, arachidonic acid was added at the concentration of 10 μM. The reaction was allowed to run for further 15 minutes. Then, the reaction was stopped by acidifying the medium.

E2 prostaglandines, produced and released into the supernatant, were then counted by a commercially available (AMERSHAM) specific immune enzymatic test.

In order to evaluate the activity on COX2, the J 774.2 cells were treated with aspirin (300 μM) for 1 hour and then incubated with LPS (1μM) for 12 hours. Afterwards, it was utilized the same procedure as described for U 937 except that arachidonic acid was not added.

The results of the tests are shown in Table 1.

TABLE 1

Compound	Concentration	% Inhibition	
	(μM)	COX1	COX2
indomethacin	10	82	-
	1	79	-
	0.1	69	-
AFR 408	10	0	89
	1	0	70
	0.1	0	26
AFR 405	10	0	57
	1	0	42
	0.1	3	35
AFR 406	10	55	60

	1	0	63
	0.1	12	44
AFR 500	10	38	69
	1	0	61
	0.1	0	25
AFR 206	10	3	72.9
	1	19	50.7
	0.1	14	4.9
AFR 207	10	39	76.3
	1	6	69.1
	0.1	16	17.6
AFR 209	10	1	6.5
	1	12	9.8
	0.1	3	27.0
AFR 402	10	0	63
	1	0	58
	0.1	0	36
AFR 404	10	42	71
	1	6	65
	0.1	19	48
AFR 101	10	77	83
	1	41	58
	0.1	0	25
AFR 507	10	83	73
	1	48	50
	0.1	58	7
AFR 508	10	44	70
	1	16	40
	0.1	13	12

AFR 906	10	17	77
	1	20	60
	0.1	16	35

TEST 2

Anti-inflammatory activity

The anti-inflammatory activity of AFR 906 and AFR 101 was evaluated according to the test of the inhibition of edema induced by carrageenin inoculation (50 µl of 1% suspension in physiologic solution) in a rat leg. AFR 906 and AFR 101 were administered orally at 30 min. from inoculation of the irritant agent at the concentration of 6.25 mg/Kg.

Indomethacin (2 mg/kg p.o.) was used as comparison product.

The test was carried out by using 12 animals for each group of treatment. The activity was evaluated by measuring the volume increase of the leg with a pletismometer.

The result of the test are shown in Table 2.

TABLE 2

	basal	30'	1h	2h	4h	6h
controls	0.82	0.96	1.04	1.31	1.46	1.35
AFR 101 (6.25)	0.83	0.95	1.01	** 1.15	** 1.25	** 1.20
AFR 906 (6.25)	0.82	0.94	0.98	** 1.16	** 1.24	** 1.21
indomethacin (2)	0.82	0.91	* 0.92	** 1.09	** 1.19	1.25

TEST 3

Analgesic activity

The activity of AFR 906 and AFR 101 were evaluated with the Randall & Selitto procedure by testing the pain test caused by a pressure on the inflamed rat leg. Pain was measured with an analgesimeter as the pressure (grams) that, applied to the inflamed leg, caused the animal to react.

The inflammatory hyperalgesia was induced by injecting brewer yeast (5%) under skin into the left leg of the rat. AFR 906 and AFR 101

were administered intraperitoneally at a dose of 12.5 mg/kg, 2 hours after the yeast administration.

The test was carried out by using 6 animals for each group of treatment. Indomethacin (2 mg/kg i.p.) was used as comparison drug. The activity of the compound under evaluation was measured as ability to rise the pain threshold.

The results of the test are shown in Table 3.

TABLE 3

Compound	Dosage	Relief (average ± D.S.)	
	(mg/Kg i.p.)	basal	+ 3 h from yeast
control	-	177 ± 19	159 ± 14
indomethacin	2	177 ± 22	270 ± 51**
AFR 906	12.5	177 ± 21	216 ± 36*
AFR 101	12.5	175 ± 21	274 ± 44**

** $p < 0.01$, * $p < 0.05$ compared to the control.

TEST 4

Activity on gastric mucosa

The ulcerogenic activity of AFR 906 and AFR 101 were evaluated on the gastric mucosa of rats treated by oral route with a single administration (6.25, 12.5, 100 and 200 mg/kg) of the compounds under evaluation.

Indomethacin was used as comparison drug (5 and 10 mg/kg).

After treatment, the animals (7-9 in each group) were maintained on an empty stomach for 17 hours (with free access to water) and then sacrificed. The gastric mucosa was examined to value the possible presence of lesions that were classified with a score of from 0 to 4 depending on the severity.

The results of the test are shown in Table 4.

TABLE 4

Compound	Dosage (mg/Kg p.o.)	rats with ulcer (%)	lesions severity (score average in animals with ulcers)
AFR 906	6.25	0	0
	12.50	0	0
	100.00	0	0
	200.00	0	0
AFR 101	200.00	38	1.7
	50.00	20	2
indomethacin	5.00	14	3
	10.00	86	3.5

TEST 5

Systemic toxic effects

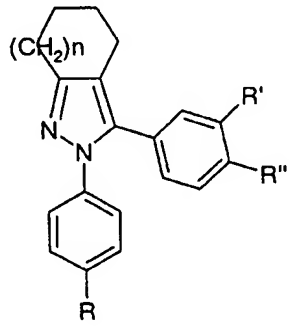
Systemic toxicity of AFR 906 and AFR 101 were valued in rat according to a variation of the Irwin test. The AFR 906 compound is devoid of behavioural and toxic effects up to a dose of 800 mg/Kg after intraperitoneal and oral administration.

The first toxic effects of AFR 101 (such as, for example, reduction of spontaneous activity, non coordination of movements and reduction of respiratory rate) become manifest at a dose of about 400 mg/Kg by both intraperitoneal and oral route.

100% of treated animals showed lethal effects at a dose of 800 mg/Kg via intraperitoneal route.

CLAIMS

1. A pharmaceutical composition comprising a diaryl-cyclomethylen-pyrazole of formula



(I)

wherein

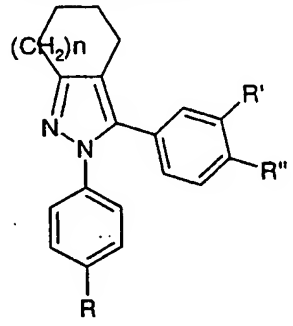
n is 0, 1, 2 or 3;

R, R' and R", equal or different each other, are H, halogen, alkyl-sulphonyl, aminosulphonyl and alkylaminosulphonyl

or a pharmaceutically acceptable salt thereof,

together with at least a pharmaceutically acceptable carrier.

2. A diaryl-cyclomethylenpyrazole of formula



(Ia)

wherein

n is 0, 1, 2 or 3;

R, R' and R", equal or different each other, are H, halogen, alkyl-sulphonyl, aminosulphonyl and alkylaminosulphonyl,

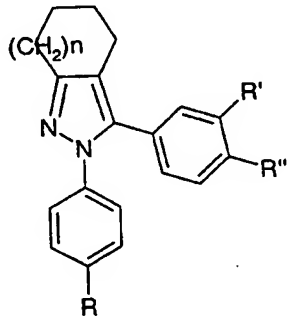
or pharmaceutically acceptable salts thereof,

provided, however, that

a) when n is 1, and two of R, R' and R" are hydrogen, the third is not hydrogen or chlorine; and

b) when n is 3, at least one of R, R' and R" is not hydrogen.

3. A compound according to claim 2, wherein n is 0, 1 or 2.
4. A compound according to claim 2 or 3, wherein halogen is fluorine or chlorine.
5. A compound according to any one of claims of from 2 to 4, wherein the alkyl chain of the alkylsulphonyl and alkylamino sulphonyl has of from 1 to 6 carbons.
6. A compound according to any one of claims of from 2 to 4, wherein the alkyl chain of the alkylsulphonyl and alkylamino sulphonyl has of from 1 to 3 carbons.
7. A compound according to any one of claims of from 2 to 6, wherein the alkyl chain is methyl or cyclopropyl.
8. A process for preparing a compound of formula (I)



(I)

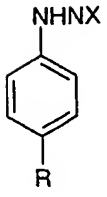
wherein

n is 0, 1, 2 or 3;

R, R' and R", equal or different each other, are H, halogen, alkyl-sulphonyl, aminosulphonyl and alkylaminosulphonyl,

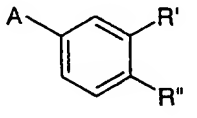
or pharmaceutically acceptable salts thereof,

wherein a compound of formula



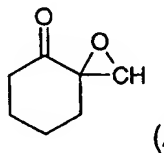
(II)

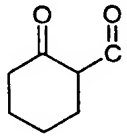
where X is H or cycloesilidene , and
R has the above mentioned meanings, is reacted with a compound of formula

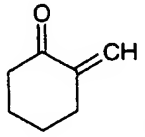


(III)

where R and R" have the above mentioned meanings and A is selected from the group comprising COHal, A', A" and A"'



(A'),


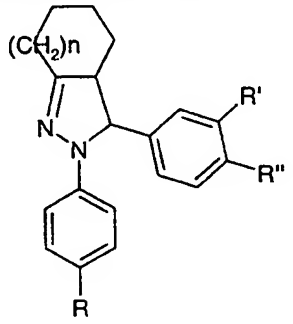
(A"),


(A"')

where Hal is halogen,
and, when desired, the so obtained compound of formula (I) is transformed into a pharmaceutically acceptable salt thereof.

9. A process according to claim 8, characterized in that, when X = H, this reaction is carried out in a solution of a suitable polar diluent and in the presence of a organic or mineral acid at a temperature of from 0 to 120°C.
10. A process according to claim 9, characterized in that the reaction is carried out at a temperature of from 60 to 80°C.
11. A process according to any one of clams 9 and 10, characterized in that the diluent is a lower aliphatic alcohol.

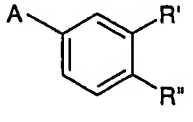
12. A process according to claim 11, characterized in that, when A = A' and X is hydrogen, the reaction is carried out in the presence of glacial acetic acid.
13. A process according to claim 11, characterized in that when A = A" and X is hydrogen, the reaction is carried out in the presence of sulphuric acid.
14. A process according to claim 11, characterized in that when A = A"' and X is hydrogen, the reaction is carried out in the presence of hydrochloric acid, to give the compound of formula (IV)



(IV)

from which the corresponding compound of formula (I) is prepared by treating with a weak oxidant.

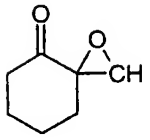
15. A process according to claim 14, characterized in that the weak oxidant is bromine in water.
16. A process according to claim 8, characterized in that, when A is COHal and X is cyclohexylidene, the reaction is carried out in the presence of anhydrous tetrahydrofuran at a temperature of from -70°C to 20°C.
17. An intermediate compound of formula



(III)

wherein

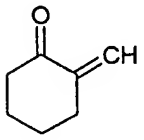
A is



and

R' is H, Cl or F and R" is alkylsulphonyl or fluorine, or

A is

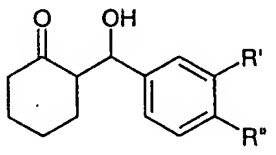


and

R' is H and R" is alkylsulphonyl.

18. A compound according to claim 17, wherein the alkylsulphonyl is methylsulphonyl.

19. An intermediate compound of formula

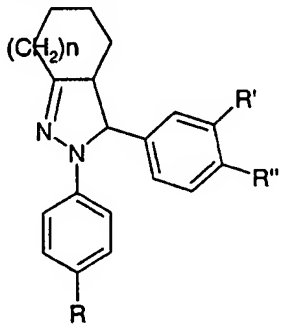


(V)

wherein R' is H and R" is alkylsulphonyl.

20. A compound according to claim 19, wherein the alkylsulphonyl is methylsulphonyl.

21. An intermediate compound of formula



(IV)

wherein n = 1, R is metylsulphonyl, R' is hydrogen and R'' is chlorine.